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Case review

Sudden death in custody due to pituitary apoplexy during long restriction in a sitting position: A case report and review of the literature

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ABSTRACT

Pituitary apoplexy is an uncommon clinical emergency arising from hemorrhage into or infarction of a pituitary adenoma. The most common presentation is sudden headache, visual field defects and signs of hypopituitarism. It usually occurs in the age group from 20 to 50 years and affects more male than female. Sudden death due to pituitary apoplexy without common symptoms is rarely reported. Here, we described a scarcely-reported case of sudden death in custody caused by pituitary apoplexy resulting from stress-induced hemorrhage of gonadotroph adenoma, a kind of pituitary adenoma, without common clinical symptoms. In this case, a 49-year-old man was restrained in a sitting position for 4 days and died unexpectedly. At autopsy, external examination showed free of trauma. Destruction of bony structure and a circumscribed pituitary tumor were observed in sella turcica. Immunohistochemically, the tumor cells were particular positive for follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thus clarifying the presence of a pituitary gonadotroph adenoma. We provide the case description and a short review of pituitary apoplexy and pituitary adenoma as a rare cause of sudden death.

1. Introduction

Pituitary adenoma is uncommon, constituting approximately 10–25% of primary intracranial tumors.[1–3] Pituitary apoplexy (PA) is an acute and potentially life-threatening complication of pituitary adenomas with a peak incidence occurring in middle-aged, male patients, characterized frequently by sudden severe headache, visual deficits, ophthalmoplegia and hormonal dysfunction attributed to rapid enlargement of the adenoma following hemorrhage or infarction.[4–6] Its exact prevalence is unknown, and greatly depends on the method of surveillance and autopsy reporting. A meta-analysis epidemiological research on pituitary apoplexy has found an overall pituitary adenoma incidence of 1.6–12.8%.[4,7,8] Gonadotroph adenoma is a kind of pituitary adenoma with extremely low incidence. Also, clinical cases and scientific studies on gonadotroph adenoma-induced pituitary apoplexy has also gained less attention compared with the other causes of pituitary apoplexy, perhaps because it is usually observed in the absence of pituitary hormonal dysfunction and lack of related specific clinical features.[9] Here, we report an unusual case of a 49-year-old man who died unexpectedly during the prolonged immobilization in a sitting position, due to stress-induced pituitary gonadotroph adenoma apoplexy.

2. Case report

A 49-year-old man had been detained in custody for questioning. He was restrained in a sitting position for four days on a fixed metal chair. On the 4th day, he became weak and subsequently unconsciousness. Emergency services were summoned and he was transported to hospital. Resuscitation was failed and he passed away in hospital. The man had no previous medical history of disease.

Forensic autopsy was carried out 45 h after death. External examination showed a well-nourished adult man. Both wrists had several horizontally oriented parallel linear contusions. Four

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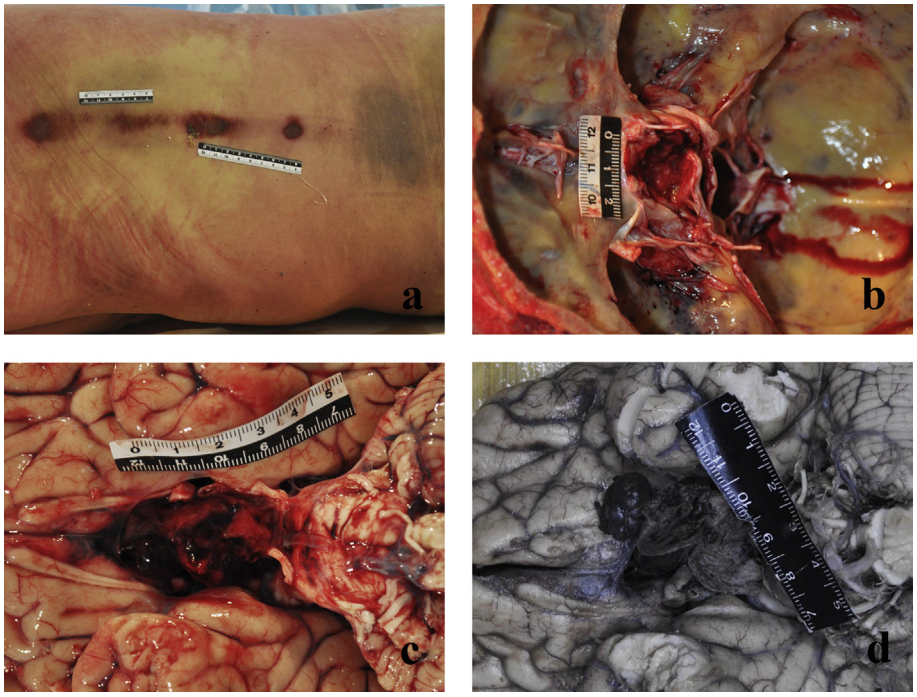

Fig. 1. Important gross appearances of autopsy findings (a) abrasions found on the lumbodorsal vertical area on the victim; (b) destruction of bony structure of the sella turcica; (c) spindle-shaped pituitary tumor with an integrated capsule; (d) cut surface of tumor appeared tan-red. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

parchmented abrasions were found on the lumbodorsal vertical area, the top-down measuring 6.0 cm × 2.8 cm, 5.2 cm × 2.0 cm, 5.8 cm × 2.5 cm and 2.0 cm × 1.5 cm, respectively (Fig. 1a). After incision of skin nearby the abrasions on his back, no subcutaneous hemorrhage was seen; and microscopically, the significant congestion and dilatation of the subcutaneous blood vessels were observed, and a few of neutrophils, lymphocytes and monocytes were seen in the tissue near the blood vessels.

On internal examination, the weight of the heart, left lung, right lung, liver, kidneys and spleen was 400 g, 600 g, 750 g, 1400 g, 300 g and 320 g, respectively, and the cut sections were unremarkable. The brain weighed 1500 g. The bony structure of sella turcica was partially destroyed (Fig. 1b), and a well, demarcated, soft, spindle-shaped pituitary tumor with an integrated capsule (Fig. 1c) was present. The tumor measured 3.0 cm × 2.0 cm × 2.0 cm and showed marked suprasellar extension and adhesions to the surrounding substantia ossea of the sella turcica. Its cut surface appeared tan-red (Fig. 1d). Microscopically, the tumor showed multiple hemorrhagic foci, degenerative changes and necrosis associated with capillary proliferation (Fig. 2a). The residual tumor tissue was mostly chromophobic and composed of cell nests, trabeculae, as well as cells with eosinophilic cytoplasm in a variety of shapes. Characteristically, the tumor showed unique morphology marked by many chromophobic spindle cells arranged in “pseudo-rosette” patterns (Fig. 2b). Immunohistochemistry showed strong immunostaining for synaptotagmin (Syn), chromogranin A (CgA), CD_{56}, which are the sensitive indicators of neuroendocrine tumors. Weak positive reaction was obtained for follicle-stimulating hormone (FSH) (Fig. 2c) and luteinizing hormone (LH) (Fig. 2d), indicating that the tumor was a gonadotroph adenoma. Furthermore, the Ki-67 labeling index (Ki67-LI) ranging from 2% to 3% indicated the lower activity. Markers such as CD_{31}, CD_{34} and Factor Ⅷ denoting tumor angiogenesis were negatively expressed. Other tumor markers including growth hormone (GH), adrenocorticotropic hormone (ACTH), prolactin (PRL) and thyroid stimulating hormone (TSH) could not be detected in the tumor tissue in this case.

Toxicological analysis of blood, liver and stomach contents done by GC-MS excluded the presence of drugs and poisons. The postmortem biochemistry examination of heart blood showed elevated myocardial and liver enzymes spectrum, and hormones secreted by pituitary gland were in the normal range (Table 1).

Scene reconstruction with the help of prison wardens showed that the victim was restrained on the chair (Fig. 3) and that his arms and wrists were fastened behind the chair. It was also reported that the detainee was violent and scratched his back vigorously against the chair, which explained the abrasions on the skin along his vertebral column. The reconstruction of the scene corresponded exactly with the localization of the injuries seen in autopsy.

The cause of death was pituitary apoplexy induced by hemorrhage of gonadotroph adenoma. The agonizing stress, emotional agitation and prolonged restraint contributed to the death.

3. Discussion

Almost all cases of pituitary apoplexy result from pituitary adenoma, a kind of benign tumor of pituitary gland. It commonly occurs when pituitary adenomas bleed internally, causing a rapid increase in size or when the tumor outgrows its blood supply which causes tissue necrosis and subsequent swelling of the dead tissue.[10] In an analysis of incidentally found pituitary tumors, apoplexy occurred in 0.2% of cases annually, but the risk was higher in tumors larger than 1 cm (macroadenomas) and tumors that were growing more rapidly and extensively.[11]

Pituitary adenoma is several times more likely to bleed than any other kinds of brain tumors and there are different possible mechanisms by which a tumor can increase the risk of either infarction or hemorrhage.[11] Pituitary gland normally derives its blood supply from vessels that pass through hypothalamus, but tumors develop a blood supply from the nearby inferior hypophyseal artery that generates a higher blood pressure, possibly accounting for the risk of bleeding. Tumors may also be more sensitive to fluctuations in blood pressure, and blood vessels may

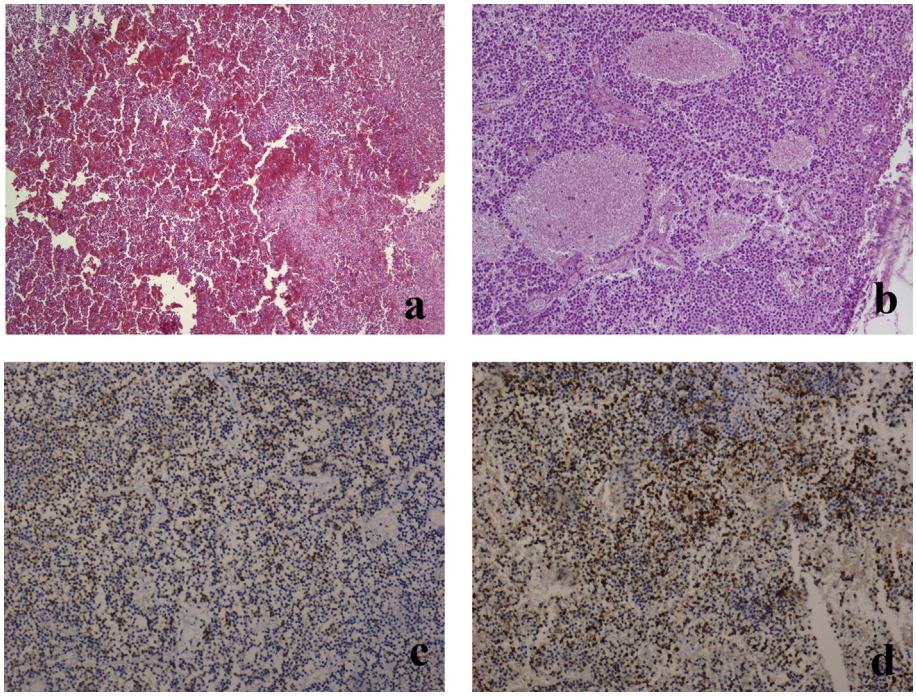

Fig. 2. Views of gonadotroph adenoma (a) multiple hemorrhage, degeneration and necrosis in tumor tissue (H&E × 100); (b) chromophobic spindle cells arranged in "pseudorosette" patterns (H&E × 200); (c) positive reaction for FSH (FSH × 100); (d) positive reaction for LH (LH × 100).

show structural abnormalities that make them vulnerable to damage. It has been suggested that infarction alone causes milder symptoms than either hemorrhage or hemorrhagic infarction.[12] Larger tumors are prone to bleeding, which can possibly account for its higher risk of undergoing apoplexy and severe syndromes.[12] Following apoplexy, the pressure inside sella turcica rises, and surrounding structures such as optic nerves and contents of the cavernous sinus are compressed. Clinical presentations of apoplexy may vary from asymptomatic to severe signs and symptoms due to pressure effects on the surrounding tissues or the hemorrhage-induced pressure.[3,5,13–15] The following may occur: impaired vision, severe headache, diplopia, hypopituitarism, ophthalmoplegia, diabetes insipidus and hormonal dysfunction.[3,5,13–16]

Table 1
Results of postmortem examination of heart blood.

Test items	Results	Reference range
Myoglobin (MB)	2342.70 ng/ml	17.40–105.70 ng/ml
Creatinine kinase, MB isoenzyme (CK-MB)	310.0 ng/ml	0.3–4.3 ng/ml
Cardiac troponin I (cTnI)	102.00 ng/ml	0.00–0.04 ng/ml
Glutamic pyruvic transaminase (GPT)	10,000 U/L	0–41 U/L
γ-Glutamyl-transpeptidase (γ-GT)	175 U/L	0–55 U/L
Creatine kinase (CK)	86,873 U/L	24–195 U/L
Lactic dehydrogenase (LDH)	68,958 U/L	0–247 U/L
Total bilirubin (TBIL)	25.3 μmol/L	3.4–20.5 μmol/L
Direct bilirubin (DBIL)	14.4 μmol/L	0.0–6.8 μmol/L
Estradiol (E2)	312.00 pg/ml	20–75 pg/ml (male)
Follicle stimulating hormone (FSH)	6.97 mIU/ml	1.27–19.26 mIU/ml (male)
Luteotropic hormone (LTH)	1.90 mIU/ml	1.24–8.62 mIU/ml (male)
Growth hormone (GH)	1.5 μg/L	0.3–3.0 μg/L (male)
Adrenocorticotropic hormone (ACTH)	4.4 pmol/L	1.1–11.0 pmol/L
Prolactin (PRL)	12.44 ng/ml	2.64–13.13 ng/ml (male)
Thyroid stimulating hormone (TSH)	1.26 uIU/ml	0.35–4.94 uIU/ml
Carcinoma embryonic antigen (CEA)	4.23 ng/ml	0.00–5.00 ng/ml

Most pituitary adenomas are restricted to sella turcica; however, gonadotroph adenoma may grow invasively into suprasellar, parasellar or contiguous structures.[9,17] Hence, gonadotroph adenoma may be more likely to undergo pituitary apoplexy than any other

Fig. 3. The iron chair with straight back and screwed to the floor.

kinds of pituitary adenomas, and symptoms and consequences of this apoplexy may be more severe and fatal. It is very unusual for gonadotroph adenoma to undergo severely spontaneous hemorrhage without any symptoms or signs, which can lead to the consequent fatal apoplexy and death.

The presence of gonadotroph adenoma can be difficult to be recognized because of the absence of obvious endocrine abnormalities.[9] In our case, the gonadotroph adenoma of the deceased was a silent macroadenoma. Specific hormonal expression by the adenoma was detected by immunocytochemistry-staining only. Biochemical results showed normal levels of blood hormone contents secreted by pituitary gland. Hence, systemic autopsy, histopathological and immunohistochemical examinations are of great importance to disclose the existence of gonadotroph adenoma. In addition, the absence of acute signs and symptoms made the medicolegal investigation more difficult. It could have been easier to conclude positional asphyxia death when only taking into account the prolonged restraint. All in all, systemic autopsy, histopathological and immunohistochemical examinations, as well as biochemistry examinations must be performed, and attention cannot be focused solely on signs, symptoms and scene evidence.

In this case, the size of the adenoma was large enough to induce pressure on important functional zones such as hypothalamus and brain stem, resulting into disturbance of consciousness or even central respiratory and circulatory disorders. Marked extensions into the suprasellar region suggest that the tumor was invasive and thus contributed to the compressive effect on vital cerebral structures. Hemorrhage into the adenoma and increased pressure further impaired blood supply to the tumor tissue leading to necrosis.[11] The consequent pressure-induced cerebral edema could also contribute to the functional damage of the brain. So, the disturbance of consciousness, central respiratory and circulatory disorders and the rapid death masked the classical signs and symptoms.

Hemorrhage into the tumor was apparently caused by higher blood pressure, fluctuations in blood pressure and structural abnormalities of the blood vessels within.[12] In this case, prolonged interrogation and restriction in an uncomfortable position could cause severe psychological stress on the victim, induced a rise in the blood pressure which could returned to normal level afterward. As a result, fluctuations of blood pressure at the least in part explained the bleeding of the tumor and resulting fatal pituitary apoplexy under these circumstances.

At present, symptomatic pituitary apoplexy is easily diagnosed clinically. However, subclinical pituitary apoplexy, with no prior history of adenoma, may be misdiagnosed as ruptured intracranial aneurysm, etc.[6,18,19] In previous retrospective studies, the diagnosis of pituitary apoplexy is clinically suspected and then confirmed by pathological findings, radiology or immunoassay.[6,20–22] However, in medicolegal investigations, a comprehensive, detailed forensic examination, including autopsy, toxicological analysis, immunohistochemical examination is of utmost importance to ascertain the type of pituitary adenoma and confirm apoplexy.

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Conflict of interest
None.

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